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2003: The Year in Review

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In this article, I would like to share my observations from the presentations, discussions, and written materials presented at the WilBio conferences during 2003. Obviously, there has been other input from a constant stream of press releases, articles, email communication, and most importantly, conversations with key individuals in industry, academia, and the FDA.

In general, the industry has gone through another of its realignment periods, where much was learned, but a lot of restructuring and refocusing took place. Driven by the need to keep the doors open, small to medium sized firms had to do some severe belt tightening, or completely redefine themselves as to technologies, products, and personnel. Many of the larger firms reevaluated their product pipelines, and then made the changes they felt were necessary to assure future revenues, or to make themselves attractive merger partners.

Numerous large mergers took place with some that were the largest the biopharmaceutical industry has ever seen. In addition, several medium-sized companies merged, or otherwise found strategic alliances that energized their product pipelines, or simply provided the cash they needed to keep going.

Antibody products did very well with a number of blockbusters receiving license approval in 2003. Humanized and human molecules have truly made antibody products viable therapies, and have blazed a trail for other product types to follow. The newer products, such as viral gene vectors and cellular therapies, can expect to follow a similar path to the one taken by antibodies. It took over 15 years for antibodies to really become successful, and there were several periods in which earlier successes turned into major disappointments. It's no wonder the regulators are so cautious with these newer therapies, since they've learned how much must still be experienced before the problems can even be identified with a new type of biological product.

Photo courtesy of Millipore Corporation

With a massive amount of accumulated data, antibodies and recombinant proteins are also leading the way toward what is hoped will be fully characterized, and possibly comparable, products. If there is to be a "generic biological," the first will surely be an antibody.

The analytical techniques have become so powerful and available that the problem now seems to be one of figuring out what to do with all of the data. The clinical chemists can come up with the technique, and they can generate tons of data, but what does it all mean?

Facilities and Production Capacity

Facilities are getting bigger and costlier, with price tags reaching a billion dollars. They are also becoming more automated and flexible in their operational capabilities. Most firms really don't know what they will be producing in a facility when they start the design, and so they need to build something that will accommodate a number of scenarios.

In general, facilities are either built to handle development, early-phase clinical products, or both late-phase and licensed products. While some firms still argue that a late-phase clinical facility should not be used to manufacture licensed products, this belief seems to be giving way to practical necessity and good design. There are just too many products and possible scenarios to build a facility for a single product, or even a single manufacturing stage.

In 2003, a number of the mergers were undertaken to obtain manufacturing capacity for anticipated products. Even with the sharp increase in construction that we have seen over the last two years,

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there never seems to be enough production capacity, or at least, not enough of the right type.

There has also been a sizable increase in the amount of contract manufacturing capacity, but again, there never seems to be enough. When I am asked if a company should build its own facility, seek outside contractors, or form strategic alliances to gain additional production capacity, I answer: "Yes."

Obviously, there are other ways to reduce the need for manufacturing capacity. First, the people in research can go back to the molecular drawing board and increase the level of expression. Traditional cellular subcloning can also prove helpful, but far more can be done by optimizing the expression system. Chemical or biochemical expression enhancement and media optimization certainly play a key role, and much can be done to improve product concentration and quality by manipulating the feed and harvest strategy.

In addition, the continuous processing, or perfusion model should be considered as a means of reducing bioreactor capacity, although there will be an increase in the vessels needed to handle media and harvest materials. While perfusion has been used successfully in many applications, including those for licensed products, it is often ruled out as too complex and difficult to validate. Again, the examples are out there for any group to emulate, and the regulators are very comfortable with the concepts.

Facility designs are not only becoming more flexible, but more automated, validatable, and energy efficient. There is more use of unclassified, or "grey," space, where a specified air quality does not have to be maintained. This technique is saving a tremendous amount of energy that would be needed for air handling, plus the labor and time associated with cleaning and maintaining classified space. Steam-in-place, clean-in-place, and other utility systems have been optimized in their flexibility, validatability, and reliability.

The biggest improvements sought today are in decreasing construction lead times. While typically more expensive, modular processing and utility systems are being used more and more in the newer facilities. This construction practice can yield significant savings in the time it takes to install, integrate, commission, and validate these primary systems, and the cost of such timesavings can far outweigh the added cost for the initial equipment.

While some firms are still hoping to achieve paperless manufacturing, few are seriously moving in this direction. Despite all of the advances in electronic signature and security technology, paper records are still desired for many functions. It is hard to say when, or if, electronic batch records will become commonplace.

Still, much has been done to build modern communication and data sharing capabilities into these new facilities. Machine / operator interfaces are far more user friendly and provide much more information, functionality, and verifiability. Operating procedures, process data, troubleshooting guides, and process recipes can all be made available for operator use, process verification, and batch record input. More facilities are being run from centralized data storage and processing systems, or distributed control systems (DCS), where the processing skids and modules require less "smarts," or actual control systems on them. Instead, the skids come equipped with smart control devices and transmitters, and in some cases, the signal transmitter handles much of the local control function.

Transgenic Production

While a cGMP facility would still be needed for processing the harvested material, purification, formulation, and filling, it would not be needed for the production portion of the process. Furthermore, if the expression claims are real, and a large amount of material could be made in a single animal or plant, transgenic protein production could provide a viable method for meeting the industry's long-term production needs.

So far, we've seen technologies that produce proteins at very high concentrations in goats, corn, tobacco, insect larvae, pigs, and eggs. The purification issues have been worked out, but of course, there are still glycosylation issues that must still be resolved with the non-animal systems. Advanced cloning techniques have made animal production feasible, with the ultimate goal in some firms to move their expression capabilities into cows.

The biggest problem with plant systems appears to be their containment, or preventing genetically modified material from getting into other crops. While a number of solutions have been proposed and tested, the most interesting was the concept of a BSL-2 greenhouse. Yet another major problem is in processing the harvested plant material and extracting the protein. Suitable, sanitary hardware has had to be custom made with designs adapted from agricultural and dairy equipment.

Similar issues reside with the animal derived materials, where feed has to be specially prepared and stored, plus animal waste must be disposed of without contaminating groundwater or the surrounding property. Dead animals, and much of the solid waste materials have to be incinerated, or disposed of in a way that no material could get into the food chain.

Defining regulatory responsibility for these products is another perplexing matter. Different stages of the production process will most likely be regulated by different agencies, or by combinations thereof. At various points, the USDA, Center for Veterinary Medicine, CBER, CDER, or almost any combination of these agencies could be involved.

Raw Materials

Although an often-neglected portion of the overall development plan, the raw material acquisition, qualification, quality control, and management plan must be integrated into the earliest phases of product development. Companies are still having problems with cell lines that were manufactured with undefined and untraceable components, plus animal sourced materials that may not have been properly screened for adventitious agents. In addition, companies discover that a critical component used in early development cannot be obtained from a qualifiable vendor, or it won't be available in the quantities needed for large-scale production. If a company wants to delay the development of a product, putting off the raw materials plan is an

excellent way to do it.

Raw material programs require extensive planning and internal communication to ensure each material will be available longer term, its source can be verified, its manufacturers can be qualified, its storage and stability can be validated, and its use can be tracked and forecasted.

Determining the amount and frequency of testing for each raw material can prove equally daunting. Some materials only need simple identity tests, while others require additional testing with USP methods. Still others require extensive testing for adventitious agents, mycoplasma, bacterial contaminants, and cell growth promotion. It takes a dedicated team of process development, research, production, QA/QC, and materials management personnel to make sure that the necessary raw materials will be available when they are needed.

Contract Services

As companies work on more products at different stages of development, they are learning that they cannot handle all of their research, testing, development, and production functions internally. More of this work is being contracted to independent contract service suppliers, or to strategic partners. As a result, the contract services industry is growing rapidly, and it appears that the better firms cannot keep up with the demand for their services.

Many of the actual biotech companies are deciding that they can earn revenue and build capabilities by offering contract services to other firms. While biotech firms have frequently sold contract research services to earn cash, today the services certainly could include cell banking, process development, testing, production, purification, formulation, and vialing. In addition to using their new biopharmaceutical facility to develop or produce their own products, companies are immediately offering any excess capacity to other biotech firms and strategic partners.

When considering contract services for the biopharmaceutical industry, we can't neglect those who provide consulting, engineering, construction, validation, legal, maintenance, and even less obvious services. Biopharmaceutical facilities have been a booming business for many engineering firms who have not had much work from the microelectronics, power, and petrochemical industries. There are essentially five engineering firms that are dominating the large facility projects, plus a number of smaller firms who are doing very well on the smaller projects, as well as the continual upgrade and maintenance projects that must be done. Still other firms exist solely on validation work.

The contract testing business is absolutely phenomenal, where almost any firm that puts a qualified toe into the water can build a substantial business. Again, it appears that the better firms are turning away work as they attempt to satisfy a smaller number of large clients.

The contract production market is dominated by a handful of companies with large, cGMP facilities. However, a number of smaller firms are attracting a lot of overflow business that is highly specialized, or is at a smaller volume than the larger firms want to handle. Viral manufacturing is still quite difficult to acquire, since the established firms are busy, and the larger contract companies typically don't want viral products in their facilities. Contract vialing and cGMP plasmid production are also in demand and are relatively hard to find.

Baculovirus Expression and Insect Cell Culture

While no product made with this technology has yet to be licensed, the industry is reaping tremendous benefits from this incredibly powerful protein expression technology. With the original production patents running out, more firms will probably pursue products they can make in this manner. It is still one of the fastest and most productive protein manufacturing techniques available, and it lacks the potential safety issues that arise with the use of mammalian cells. In addition, insect cells have been shown to provide some of the post-translational processing needed for glycoprotein manufacturing, which makes them preferable expression candidates to yeast and bacteria. However, many biotech products don't have to be fully functional glycoproteins, and the development of such products is where this technology can best be applied.

Product Development Life Cycle

As biological products and production technologies have matured, the key issues have moved from cell culture based problems, to those associated with purification, then formulation and stability, and finally characterization. At this point, comparability becomes the ultimate hurdle as organizations dream of making process or product improvements without having to conduct costly human trials. If indeed, biological product comparability becomes a reality, then production costs could drop dramatically and we could eventually see a generic biologics industry as product patents expire. The most mature biologics, such as cytokines and antibodies, have certainly followed the path described above, and we can expect the newer products to experience a similar chain of events.

While antibodies have been through several rough periods, they have now progressed to the endgame where characterization and comparability are the primary challenges. However, product comparability is still a ways off, and the most promising data, from the largest firms with the best-understood products, has not proved convincing.

On the other hand, viral products have pretty much worked their way through the cell culture and yield issues, but are still only partially through the purification issues, where many organizations are still using cesium chloride gradients. They are surely running headlong into the questions associated with formulation and stability, with characterization issues barely being addressed and the topic of comparability not even being discussed.

Then there are cellular products. Here, the initial processing issues are still an open book, and purification is often sidestepped. Formulation is rudimentary, and stability isn't an issue since the product has to be administered almost immediately. When talking about characterization, you must first try to tie down what the product is. In

many cases, the final preparation is a heterogeneous population of cells with a cocktail of protein stimulants. It turns out that some, or possibly all, of the components may have a therapeutic effect, or it may be the specific combination that does the trick. To make matters more interesting, it may or may not matter if the primary cells in the mixture are alive. While the story isn't quite as complex for all cellular products, it is easy to see why these products are so difficult for organizations to characterize, and for CBER to regulate.

Product Discovery

Genomics has given way to proteomics, and now, to functional proteomics. There is a vast industry that has been developed to identify, produce, and rapidly screen a countably infinite number of proteins for use in human therapy. From this work, an additional industry has been assembled to design and build the analytical tools that are needed, and to manage and "mine" the data that is produced.

While this work has tremendous promise and is already yielding results, the task is mind-boggling. Determining what a protein does and how it works is hard enough, but then figuring out all of the steps that lead up to why and how it is produced, what turns its production off, and how it interacts with other proteins, make this a formidable task indeed.

As this portion of the industry advances, we can expect to see incredible spin-off technologies, some of which are already being applied in process monitoring and the ever-challenging field of product characterization.

In Summary

2003 was a year of uncertain financial times, but a favorable regulatory climate. Many small companies struggled since money was tight, but they learned how to live without venture capital and work more effectively with other biotech firms. Venture money assumed a different role by financing later-stage development, and more funding had to come from private investment and corporate deal making.

The people making antibodies were on a roll, and a significant number of products were licensed. It was as though all the years of hard work had paid off, and we really knew how to produce antibodies that made sense, while making them relatively efficiently and getting them to work *in vivo*.

Good news arrived in the fall for viral gene vectors with a product approval in China and a fast-track approval process for a US product. In addition, several cellular therapies continued to move closer to licensure.

We've apparently learned to design facilities that are more flexible, easier to maintain, and can be completed in less time. In addition, companies are being more creative in how they acquire additional production capacity, plus the raw materials and contract services they need.

Especially in the fall, there was a flurry of activity for the companies that supply services and products to the biotech firms, and the construction industry was busy throughout the year. Momentum appears to be building with increased consumer, and industry, confidence, and it looks like 2004 could be a very productive year.